Remarks/Arguments

Status of Claims

Claims drawn an isolated human G protein coupled receptor (motilin receptor) comprising an amino acid sequence set forth in either SEQ ID NO: 3 (MTL-R1A), or SEQ ID NO: 5 (MTL-R1B), or encoded by a nucleotide sequences set forth in SEQ ID NOS: 1, 2 or 4, and a method for determining whether a ligand is capable of binding to a human motilin receptor comprising are under examination.

Claims 1, 2 and 8 have been previously presented (Amendment filed in May 2004). Claims 3 and 4 are currently amended. Claims 9 through 16 are new and presented for the first time in the instant RCE submission.

The subject matter of the newly added claims, which are drawn to a method of screening for motilin receptor ligands (claim 9), nucleic acid sequences which encode a human motilin receptor (claims 10-12), expression vectors comprising the disclosed nucleic acids (claims 13 and 14), and host cells transfected with the disclosed nucleic acids (claims 15 and 16) are within the scope of the invention elected for examination in the first-filed application.

Claims 9 through 16 find support throughout the application as filed. For example, support for the subject matter of Claim 9, drawn to an assay method utilizing an expression vector comprising the nucleic acid sequence of SEQ ID NO:2 or SEQ ID NO: 4 can be found on page 6, lines 1 through 20, which provides a description of the high-throughput assay which was developed using the disclosed motilin receptor sequences.

Support for the nucleic acids recited in Claims 10 which includes:(a) a nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO:2, (b) a nucleic acid sequence consisting of the nucleic acid sequence of SEQ ID NO: 4, (c) a cDNA sequence encoding a motilin receptor isolated from a human thyroid library, and (d) a cDNA sequence encoding a motilin receptor isolated from a host cell transfected with the nucleic acid of SEQ ID NO: 1, can be found

on page 6, lines 29 through 35; on page 10, lines 16 through 29; and on page 11, lines 6 through 10.

More specifically, page 6 describes the two splice forms of the human motilin receptor which are disclosed and claimed in the instant application as MTL-R1A (SEQ ID NO: 2) and MTL-R1B (SEQ ID NO: 4). Page 10 describes the isolation of cDNA clones from a human thryroid library and from cells transfected with an expression vector comprising SEQ ID NO:1 by a combination of rapid amplification of cDNA ends (RACE) and reverse transcription polymerase chain reaction (RT-PCR).

Accordingly, support for the recitation of a claim drawn to a nucleic acid molecule encoding a protein according to claim 2, wherein the nucleic acid consists of a cDNA sequence isolated from a human thyroid DNA library (Claim 11), can be found on page 10, lines 16 through 29; and support for the subject matter of Claim 12, which is drawn to a cDNA encoding a human motilin receptor wherein the cDNA consists of a nucleic acid isolated from a host cell transfected with an expression vector comprising SEQ ID NO:1 can be found page 11, lines 6 through 10.

Support for the expression vectors recited in claims 13 and 14 can be found on page 7, lines 16 through 24 and in examples 2 and 3 of the disclosure. Support for the host cells recited in Claims 15 and 16 can be found on page 7, lines 25 through 34 and by the host cells exemplified in examples 2, 3, and 4 of the disclosure.

Based on the above-provided explanations it is apparent that the specification as filed fully supports the subject matter of the newly added claims. Accordingly, entry of the newly filed claims will not introduce new matter into the application.

The Rejection of Claims 1-6 Under 35 U.S.C. §102, Should be Withdrawn

The rejection of claims 1-6 under 35 USC §102(a) as being anticipated by McKee, K *et al.* (Genomics, 46:426-434 (1997) for the reasons stated in the Office Action dated February 17, 2004 was maintained.

The Office Action states that "[a]lthough, McKee *et al.* does not provide a coding sequence for the orphan receptor, McKee does provide the amino acid sequence of the claimed receptor (Fig. 1)" (Office Action, page 2). The Examiner's basis for maintaining the rejection is based on the position that "[a]pplicants provide no traversal to the Examiners Office Action

pertaining to McKee disclosing that the GPR38 receptor is characterized by a 100% query match to SEQ ID NOS 3 and 5 of the instant application" (Office Action, page 2); and the observation that the rejected claims were drawn to a specific GPCR polypeptide whose specific sequence was allegedly disclosed by McKee. For the record, it should be noted that the Examiner did not provide a sequence alignment to support the alleged 100% query matches.

The McKee *et al.* reference reports the cloning and characterization of two G protein-coupled receptors (G-PCRs) related to the growth hormone secretagogue receptor (GHS-R), from human genomic DNA libraries using a hybridization probe consisting of a fragment of the type 1a GHS-R. The deduced amino acid sequence for a virtual GPR38 receptor presented in Figure 1 of the cited reference was predicted from the nucleotide sequence of the genomic DNA clone. The alignment figure provided in Figure 1 of the cited McKee reference compares the deduced GPR38 amino acid sequence to human GHS-R type 1 a, and to an amino acid sequence deduced from a full length GPR39 cDNA clone.

Applicants respectfully traverse the allegation that the amino acid sequence provided in Figure 1 of the McKee *et al.* reference is characterized by a 100% query match to SEQ ID NO:3 (MTL-R1A) and SEQ ID NO: 5(MTL-R1B). A comparison of the amino acid sequence provided in Figure 1 of the McKee *et al.* publication reveals that the deduced GPR38 protein sequence disclosed in the reference consists of 438 amino acids. In contrast, MTL-R1A (SEQ ID NO: 3) encodes a seven transmembrane domain receptor comprising 412 amino acids and MTL-R1B (SEQ ID NO: 5) endcodes a five transmembrane domain receptor comprising 363 amino acids.

As disclosed in the specification (see page 5 lines 24 through 30 and Figure 6), MLT-R1A and MLT-R1B represent two alternatively spliced forms of the motilin receptor. More specifically, MTL-R1A mRNA is formed by joining nucleotide 901 (donor A: imperfect splice donor C/gt) to nucleotide 1703 of the genomic GPR38 clone (consensus perfect acceptor sequence ag/TG). Formation of the splice junction results in the donor supplying C and the acceptor supplying TG to form the triplet codon for leucine at position 301 of MTL-R1A. MTL-R1B mRNA is formed by joining of nucleotide 1051 (donor B: perfect splice donor CG/gt to the same consensus acceptor sequence (ag/TG). Formation of this splice junction results in the donor supplying CG and the acceptor supplying T to form the codon for arginine at position.

The difference between the deduced GPR38 sequence taught in McKee *et al.* and the motilin receptor sequences disclosed and claimed in the instant application most likely resulted from an error resolving the exon-intron boundaries present in the genomic clone. As a result the deduced amino acid sequence for the virtual protein presented in Figure 1 of the cited reference includes 27 deduced amino acids, located at positions 301-327 of the deduced GPR38 sequence, which do not occur in either the MTL-R1A or MTL-R1B amino acid sequences disclosed and claimed in the instant application.

Further, although the amino acid residues identified at positions 328 to 438 of the deduced sequence presented in Figure 1 of McKee *et al.* correspond to sequence that is present in MTL-R1A, the triplet codon for leucine at residue 301 (i.e., the splice junction) of MTL-R1A, is not taught. In addition, because McKee *et al.* does not teach any splice variants, there is no disclosure of sequence information which corresponds to the complete amino acid sequence of the MTL-R1B form of the receptor. In summary, because McKee *et al.* teaches an incorrect amino acid sequence which does not represent a 100% query match to either MTL-R1A or MTL-R1B the cited reference cannot deprive the amino acid sequences of the invention of their novelty.

Furthermore, as noted by the examiner, because McKee *et al.* does not provide the nucleotide sequence of the genomic clone from which the incorrect virtual amino acid sequence was deduced, the teachings of this reference also fails to anticipate the nucleic acid sequences which are recited in the amended claim set.

In light of the arguments provided above, and the amendments made to the pending claims, Applicants respectfully request reconsideration and withdrawal of this anticipation rejection.

The Rejection of Amended Claims 1-4 Under 35 U.S.C. §102, Should be Withdrawn

In view of the amended claims, the Examiner recast the initial rejection under 35 U.S.C. §102(a), and rejected Claims 1-4 as being anticipated by McKee, K *et al.* (Genomics, 46:426-434 (1997).

The second anticipation rejection was premised on the observation that the amended claims were directed to a motilin polypeptide and the finding that the McKee *et al.* reference, which was alleged to have 100% query match to SEQ ID NOS: 3 and 5 of the instant application, met the limitations of claim 1 to 4 absent evidence to the contrary.

As amended, the claims currently under examination are drawn to specific human motilin receptor sequences which comprise either amino acid sequences that differ from the incorrect virtual amino acid sequence presented in McKee *et al.*, and to novel: (1) nucleotide sequences encoding the disclosed MTL-R1A and MTL-R1B receptors, (2) vectors comprising the nucleotide sequences of the invention, (3) host cells transfected with the vectors and (4) method of using the disclosed sequences and host cells to screen for ligands that are capable of binding to a motilin receptor, none of which are taught by McKee *et al.*

In light of the fact that the McKee *et al.* reference fails to teach an amino acid sequence which corresponds to the correct amino acid sequence of either MTL-R1A (SEQ ID NO: 3) or MTL-R1B (SEQ ID NO: 5) Applicants respectfully request reconsideration and withdrawal of this anticipation rejection.

The Rejection of Amended Claim 8 Under 35 U.S.C. §103, Should be Withdrawn

Claim 8 was rejected under 35 U.S.C. §103 as being unpatentable over McKee, K *et al.* (Genomics, 46:426-434 (1997) in view of Weinshank *et al.* (US Patent No.: 5,155,218). Claim 8 is drawn to a method of determining whether a ligand is capable of binding to a human motilin receptor.

The obviousness rejection is premised on the Examiner's observation that McKee *et al.* state that "[t]he ligand-binding and functional properties of GPR38 and GPR39 remain to be determined" (see, Abstract) and Weinshank *et al.'s* disclosure of a method for determining whether a ligand is capable of binding to a specific GPCR. The Examiner states that the method disclosed by Weinshank *et al.* comprises the steps of: (a) transfecting test cells with an expression vector encoding a GPCR; (b) exposing the test cells to the ligand; (c) measuring the amount of binding of the ligand to the receptor; (d) comparing the amount of binding of the ligand to the GPCR receptor in test cells with the amount of binding of the ligand to control cells

that have not been transfected with the receptor; and (e) concluding that compounds that bind only to test cells are specific for GPCR.

The Examiner goes on to indicate that "[i]t would have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to use the GPR38 disclosed by McKee in the methods disclosed by Weinshank to determine which ligands were capable of binding to the newly cloned receptor" (Office Action, page 6). The Examiner also noted that "[a]lthough the nucleic acid sequence encoding the GPR38 is not disclosed, the GPR38 clone inherently has the sequence, which encodes the claimed the polypeptide" (Office Action, page 5). The Examiner further reasons that "[t]he ordinary artisan would have been motivated to use GPR38 in the methods disclosed in Weinshank because, as disclosed by McKee, the ligand-binding and functional properties of GPR38 remain to be determined" (*Id.*). The Office Action indicates that at the time of filing of the instant application, the ordinary artisan would have "easily been able to produce the transfected cells required to do the assay," and "would have had a reasonable expectation of success at assaying GPR38 for ligand binding" (Office Action, page 7).

Applicants respectfully traverse this obviousness rejection on the grounds that even if a skilled artisan was motivated elucidate the ligand-binding and functional properties of the GPR38 receptor disclosed by McKee et al, there would have been a low expectation of success. This argument is primarily grounded in the fact that because McKee et al. (1) did not disclose the nucleotide sequence of the genomic clone, and (2) provided incorrect amino acid sequence information for GPR38, it is unlikely that an artisan would have succeeded at producing host cells expressing functional GPR38 receptors.

Further, there is no evidence that the requisite nucleotide sequence was known to persons of ordinary skill in the field of the invention. It is well established, that inherency cannot be based on the knowledge of the inventor, facts asserted to be inherent must be shown by evidence from the prior art.

Neither the teachings of Weinshank *et al.'s* disclosure relating to a method for determining whether a ligand is capable of binding to a specific GPCR, or contemporaneous knowledge at the time of Applicants' invention provides the requisite sequence information

required to produce a host cell expressing a functional human GPR38 receptor. Accordingly, Applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

In summary, Applicants maintain that the amended claims are in condition for allowance and a favorable action on the merits is earnestly solicited.

Respectfully submitted,

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